The present invention provides a novel human short chain dehydrogenase. The utility of dehydrogenases is well known in the art. The Examiner argues that the claimed invention lacks patentable utility because "[t]he specification fails to show a single working example that establishes that the SEQ ID NO:8 is a member of Alcohol dehydrogenase (ADH) family, such as by an substantial sequence homology and/or functional assay of the protein." March 25, 2002 Office Action, page 3. In support of this argument that the 21612 polypeptide does not have dehydrogenase activity, the Examiner cites an Office sequence search demonstrating that the 21612 dehydrogenase shares 41.7% sequence identity with a hypothetical ribitol-dehydrongase from *C. elegans* (NCBI Accession No. T19954), and 12.7% sequence identity with an EST corresponding to a human alcohol dehydrogenase (NCBI Accession No. AA622988).

As an initial matter, Applicant notes that although the Examiner discounts the significance of the sequence similarity between the amino acid sequence set forth in SEQ ID NO:7 and the amino acid sequence of NCBI Accession No. T19954 because the overall sequence identity shared between these two proteins is 41.7%, the polypeptide of NCBI Accession No. T19954 shares approximately 64% local sequence identity and approximately 74% local sequence similarity over amino acids 2 –276 of SEQ ID NO:7. This region of the 21612 polypeptide encompasses the Pfam short chain dehydrogenase consensus sequence shown in Appendix B of Applicant's response mailed August 17, 2001. Those of skill in the art recognize that a high level of sequence identity within a functional domain of a polypeptide is a reliable indicator of polypeptide function. Therefore, the fact that the 21612 polypeptide and the dehydrogenase of NCBI Accession NO. T19954 share 74% sequence similarity within a region encompassing the 21612 dehydrogenase domain supports the conclusion that the 21612 polypeptide functions as a dehydrogenase.

With respect to NCBI Accession No. AA622988, Applicant notes that nucleotides 27-386 of this EST sequence (which is only 386 nucleotides in length) share 99% sequence identity with nucleotides 1694-2052 of the nucleotide sequence set forth in SEQ ID NO:7. Accordingly, the level of sequence identity shared between NCBI Accession

No. AA62298 and SEQ ID NO:7 supports rather than undermines the conclusion that the 21612 polypeptide has dehydrogenase activity.

Furthermore, as described previously in Applicant's response mailed November 19, 2001, the function of the 21612 polypeptide was **not** determined based on the **overall** sequence identity shared between the 21612 amino acid sequence shown in SEQ ID NO:7 and the sequences of known dehydrogenases. Rather, the function of the 21612 polypeptide was determined by comparing the 21612 amino acid sequence set forth in SEQ ID NO:7 to the functional domain consensus sequences contained in the Pfam database of consensus alignments. This analysis demonstrated that the 21612 polypeptide contained a consensus sequence for short chain dehydrogenases (Pfam Accession No. PF00106). A copy of the alignment of 21612 with the Pfam short chain dehydrogenase consensus sequence was provided as Appendix B with Applicant's response mailed November 19, 2001.

As described in Applicant's response mailed November 19, 2001, the Pfam database provides a curated collection of well-characterized protein family domains with high quality alignments. Functional domains of novel proteins may be identified by comparison with the Pfam protein family domain alignments. It is well known in the art that the presence of a consensus domain characteristic of a family of proteins having a know function may be used to determine the function of a novel polypeptide. The sequences included in the Pfam seed alignment used to create the short chain dehydrogenase consensus include proteins that have been well-characterized biochemically; for example an alcohol dehydrogenase from *Drosophila* (NCBI Accession No. P21898), several human estradiol 17 β-dehydrogenases (NCBI Accession Nos. P37059, P51659, and P14061), a human corticosteroid 11-β-dehydrogenase (NCBI Accession No. P80365), and a human 15-hydroxyprotaglandin dehydrogenase (NCBI Accession No.

In responding to these arguments, the Examiner states that Applicant's arguments are found unpersuasive "because PFAM analysis revealed that 21612 matches with a top-scoring domain for ADH-short but with low sequence similarity." March 25, 2002

Office Action, page 2. This line of reasoning by the Examiner is inconsistent with the understanding of one of skill in the art of Pfam alignments. As known to those of skill in the art (and described in the Pfam documentation available at http://pfam.wustl.edu/faq.shtml), Pfam alignments do not display homology between pairs of sequences but rather display the fit of a particular query sequence to a particular protein family model. Thus the measure of the strength of a match between the query sequence and the Pfam consensus alignment is the Pfam bit score, which shows the statistical significance of the fit between the query sequence and the Pfam consensus alignment.

A Pfam "bit score" represents the log base 2 of the ratio of the probability of the sequence given the hypothesis that the sequence belongs to the protein family being modeled versus the probability of the sequence given the hypothesis that the sequence was generated according to a random background model. Thus, the bit score of 145 for the 21612 polypeptide when fit to the Pfam short chain dehydrogenase model means this amino acid sequence is 2^{145} times more likely to belong to the short chain dehydrogenase family than to contain the amino acid sequence shown in Appendix B of Applicant's Amendment mailed November 19, 2001 by chance.

Under the "Examination Guidelines for the Utility Requirement" (MPEP § 2107) "[t]he examiner's decision [with respect to patentable utility] must be supported by a preponderance of all the evidence of record," MPEP § 2107.02, *citing In re Oetiker*, 24 U.S.P.Q.2d 1443 (Fed. Cir. 1992). In the present case, all of the evidence of record provides strong support for the conclusion that the 21612 polypeptide functions as a short chain dehydrogenase. Consequently, the preponderance of the evidence supports Applicant's asserted utility.

The Rejections Under 35 U.S.C. § 112, First Paragraph, Should be Withdrawn

Claims 63-67, 77-79, and 87-104 have been rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not provide sufficient guidance to

enable one skilled in the art to make and use the claimed invention. The rejection is respectfully traversed for the reasons described below.

The Examiner argues that the claimed invention is not enabled because "[i]t is unclear how one skill in the art would use the invention as claimed when the function of the polypeptide encoded by the nucleotide sequence of SEQ ID NO:8 is not known." March 25, 2002 Office Action, page 5. However, Applicant has shown that the 21612 polypeptide has dehydrogenase activity as described above in the arguments addressing the rejection under 35 U.S.C. § 101. Furthermore, the Examiner has presented no evidence to demonstrate that one of skill the art would doubt the credibility of Applicant's assertion that the 21612 polypeptide functions as a dehydrogenase. Accordingly, the premise on which the rejection is based, i.e. that the 21612 polypeptide does not have dehydrogenase activity, is not supported by the evidence of record.

The Examiner also argues that the specification does not provide sufficient guidance to allow one of skill in the art to make and use variants of the 21612 polypeptide having dehydrogenase activity. However, in Applicant's response mailed November 19, 2001, Applicant demonstrated that a rational scheme for determining the regions of the 21612 short chain dehydrogenase that would tolerate modification is provided. Based on the regions of the 21612 polypeptide that are conserved with other short chain dehydrogenases, and the methods provided for identifying additional residues critical for 21612 function, the skilled artisan could choose among possible modifications to produce polypeptides encodes by nucleotide sequences within structural parameters set forth in the claims and then test these modified variants to determine if they retain dehydrogenase activity.

Applicant notes that an enabling disclosure need describe the claimed invention in such a way as to enable the ordinarily skilled artisan to make and use the invention, and that this description be commensurate with the scope of the claimed invention. There is no requirement that the disclosure provide working examples of every permutation of the invention.

Nevertheless, the Examiner has maintained the rejection on the grounds that "the specification fails to disclose that any and all variants of SEQ ID NO:7 (as claimed) are capable of eliciting any ADH-like activity." March 25, 2002 Office Action, page 5. As an initial matter, Applicant has **not** asserted that every nucleotide sequence meeting the structural limitations of claims 88-92 will also encode a polypeptide having dehydrogenase activity. Rather, these claims are limited to nucleotide sequences meeting both the structural requirements of these claims (i.e. the nucleotide sequences share sequence identity with the nucleotide sequence set forth in SEQ ID NO:8, hybridize with the nucleotide sequence set forth in SEQ ID NO:8 under specified conditions, or contain a subset of the nucleotide sequence set forth in SEQ ID NO:8 or the nucleotide sequence of the cDNA insert of the plasmid deposited with ATCC as patent deposit number PTA-2170) and the functional requirements of these claims (i.e. the nucleotide sequences encode a polypeptide having dehydrogenase activity). Furthermore, as described in Applicant's response mailed November 19, 2001, the specification provides sufficient guidance to allow one of skill in the art to make nucleotide sequences falling within the structural limitations of the claims and determine whether these sequences encode polypeptides having the functional limitation of the claims. Accordingly, the scope of enablement provided in the specification is commensurate with the scope of the claims.

The Examiner also argues that the specification does not enable variants of the 21612 polypeptide on the grounds that "[i]t is general knowledge in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of the polypeptide and its tertiary structure is neither well understood nor predictable." March 25, 2002 Office Action, page 6. The premise of the Examiner's argument appears to be that Applicant must demonstrate a working example of each and every sequence falling within the limitation of the claims, and that the claimed invention is enabled only if no experimentation is required to make and use the claimed variants. This requirement is not supported by the applicable case law. The test of enablement is not whether experimentation is necessary, but rather if

experimentation *is* necessary, whether it is undue. *In re Angstadt*, 198 USPQ 214, 219 (C.C.P.A. 1976). Factors to be considered in determining whether undue experimentation is required include the quantity of experimentation necessary, the amount of guidance provided in the specification, the presence of working examples of the invention in the application, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability in the art, and the breadth of the claimed invention. *In re Wands*, 8 USPQ 2d 1400, 1404 (Fed. Cir. 1988).

Based on the guidance provide in the specification, the regions of the 21612 polypeptide that are conserved with other short chain dehydrogenases, and the methods provided for identifying additional residues critical for 21612 function, the skilled artisan could choose among possible modifications to produce polypeptides encoded by nucleotide sequences within structural parameters set forth in the claims and then test these modified variants to determine if they retain dehydrogenase activity. Although some quantity of experimentation would be required, the level of experimentation would not be undue in view of the quantity of experimentation necessary, the amount of direction provided in the specification, the state of the prior art, the presence of a working example of the invention, the level of skill of one of ordinary skill in the art, and the breadth of the claimed invention. These factors all favor a conclusion that one of skill in the art could practice the claimed invention without undue experimentation.

The Examiner also argues that the claimed invention is not enabled because the specification fails to disclose the role of the claimed polypeptides in any disease. However, the claims are not directed to methods of treating a particular disease. Rather, the claims are directed to nucleic acid molecules, host cells, methods for detecting nucleic acid molecules, and methods for producing a polypeptide. Accordingly, the arguments presented in the office action are not relevant to the subject matter claimed.

The Examiner has rejected claims 65-67 and 95-97 on the grounds that these claims encompass host cells *in vivo* and therefore Applicant must provide guidance for the use of the sequences in gene therapy and in producing transgenic animals. The Examiner argues that "gene therapy is considered a highly experimental area of research

at this time, and both researchers and the public agree that demonstratable progress to date has fallen short of initial expectations." March 25, 2002 Office Action, page 7. The Examiner also argues that "the phenotype of an animal is determined by a complex interaction of genetics and environment." March 25, 2002, Office action, page 7. However, the arguments presented in the Office Action are not relevant to the claimed subject matter because the claims are not directed to methods of gene therapy or to methods of producing a transgenic animal having a particular phenotype but instead are directed to host cells containing specified nucleic acid molecules. Methods of producing such host cells are described on pages 85-90 of the specification. Based on the guidance provided, on of skill in the art could produce the claimed host cells without undue experimentation. The proper test for the enablement of an invention is whether the specification provides enablement commensurate with the scope of what is claimed. The specification has provided sufficient guidance to allow one of skill in the art to make and use the host cells of claims 65-67 and 95-97, and therefore the enablement requirement is met.

Claims 88-92 have been rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not provide an adequate written description for the claimed invention. The rejection is traversed for the reasons described below.

The Examiner argues that the claimed invention is not adequately described because "the applicant fails to point out where in the specification it is disclosed that the polypeptide encoded by the nucleic acid molecule of SEQ ID NO:8 have any alcohol-dehydrogenase-like activity explicitly or implicitly as putatively consider by the applicant." March 25, 2002 Office Action, page 8. However, Applicant has shown that the 21612 polypeptide has dehydrogenase activity as described above in the arguments addressing the rejection under 35 U.S.C. § 101. Furthermore, the Examiner has presented no evidence to demonstrate that one of skill the art would doubt the credibility of Applicant's assertion that the 21612 polypeptide functions as a dehydrogenase.

Accordingly, the premise on which the rejection is based, i.e. that the 21612 polypeptide does not have dehydrogenase activity, is not supported by the evidence of record.

The Examiner states that the rejection under 35 U.S.C. § 112, first paragraph for lack of written description in maintained because "[t]he specification fails to disclose any and all variants of nucleic and amino acid sequences of SEQ ID NO(s) as claimed." March 25, 2002 Office Action, page 8. This statement suggests that the Applicant must disclose the sequence of each variant falling within the structural and functional limitations set forth in the claims in order to adequately describe the claimed genus of sequences. However, the requirement set forth in the office action is not supported by the "Guidelines for Examination of Patent Applications Under the 35 U.S.C. §112, ¶ 1, 'Written Description' Requirement" (66 Fed. Reg. 1099 (2001)) or the supporting case law.

The "Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, 'Written Description' Requirement" state that genus may be described by "sufficient description of a representative number of species . . . or by disclosure of relevant, identifying characteristics , *i.e.* structure or other physical and/or chemical properties." *Id.* at 1106. Furthermore, the Guidelines state that "[d]isclosure of any combination of . . . identifying characteristics that distinguish the claimed invention from other materials and would lead one to the conclusion that the applicant was in possession" of the claimed invention is sufficient to satisfy the written description requirement. *Id.* at 1106.

Applicant submits that the written description provided for the sequences recited in claims 88-92 meets this requirement. These claims recite the identifying structural characteristics that define each genus of nucleotide sequences. Claims 88-90 recite nucleotide sequences having at least 70%, 80%, or 90% sequence identity with the nucleotide sequence set forth in SEQ ID NO:8, claim 91 recites nucleotide sequences that hybridize to the nucleotide sequence set forth in SEQ ID NO:8 under specified conditions, and claim 92 recites nucleotide sequences encoding a fragment of the amino acid sequence set forth in SEQ ID NO:7 or the amino acids sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Patent Deposit Number PTA-2170,

wherein the fragment has dehydrogenase activity and consists of at least 139 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:7 of the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Patent Deposit Number PTA-2170. These structural limitations are sufficient to distinguish the claimed nucleotide sequences from other materials and thus sufficiently define the claimed genus.

Furthermore, in *Regents of the University of California v. Eli Lilly & Co*, 119 F.3d 1559 (Fed. Cir. 1997), the court held that "[a] description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." 119 F.3d at 1569. The recitation of the structural features of sequence identity with SEQ ID NO:7, hybridization with SEQ ID NO:7, or the presence of subsequences of SEQ ID NO:8 or the amino acid sequence encoded by the plasmid deposited with ATCC as Patent Deposit Number PTA-2170, where the fragments have a given minimum length is sufficient to satisfy this requirement.

Applicant has further provided the functional characteristics that distinguish the claimed sequences of the genus. Specifically, claims 88-92 recite that the variants and fragments have dehydrogenase activity. Accordingly, both the structural properties and the functional properties that characterize the claimed genus are specifically recited in the claims.

As described in Applicant's Amendment mailed November 19, 2001, the present claims are analogous to those presented in Example 14 of the Revised Interim Written Description Guidelines Training Materials. Example 14 is directed to a generic claim: a protein having at least 95% sequence identity to the sequence of SEQ ID NO:3, wherein the sequence catalyzes the reaction A → B. The conclusion in the Training Materials is that the generic claim of Example 14 is sufficiently described under § 112, first paragraph, because 1) "the single sequence disclosed in SEQ ID NO:3 is representative of the genus" and 2) the claim recites a limitation requiring the compound to catalyze the

reaction from A → B. The conclusion in the Guidelines is that one of skill in art would recognize that the Applicant was in possession of the necessary common attributes possessed by the members of the genus.

Following the analysis of Example 14, Applicant submits that claims 88-92 satisfy the written description requirements of § 112, first paragraph. Specifically, the claims of the present invention encompass nucleotide sequences having sequence identity to the nucleotide sequence of SEQ ID NO:8, hybridizing under stringent conditions to the nucleotide sequence of SEQ ID NO:8, comprising a subsequence of SEQ ID NO:7, wherein the claimed sequences encode a polypeptide having a specified activity. As in Example 14, the specification discloses the nucleic acid sequence of SEQ ID NO:1, and the claims recite a limitation requiring the compound to have a specific function (*i.e.* dehydrogenase activity). Accordingly, claims 88-92 provide the relevant, identifying characteristics that describe the claimed genus, and one of skill in the art would recognize that the inventors were in possession of the claimed invention.

In view of the above arguments, all grounds for rejection under 35 U.S.C. 112, first paragraph, have been overcome. Reconsideration and withdrawal of the rejections are respectfully requested.

The Rejection Under 35 U.S.C. § 112, Second Paragraph, Should be Withdrawn

The rejection of claim 79 under 35 U.S.C. § 112, second paragraph, has been maintained on the grounds that the claim is indefinite because it is unclear what the "instructions for use" recited in the claim are. Claim 79 was amended in Applicant's response mailed November 19, 2001 to recite that the claimed kit comprised instructions for use in the method of claim 77. Applicant submits that the metes and bounds of this claim would be clear to one of skill in the art. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Consideration Of Previously Submitted Information Disclosure Statement

It is noted that initialed copies of the PTO Forms 1449 that were submitted with Applicant's Information Disclosure Statement filed May 15, 2000 and October 15, 2001 have not been returned to Applicant's representative with the Office Action. Accordingly, it is requested that initialed copies of these Forms 1449 be forwarded to the undersigned with the next communication from the PTO. In order to facilitate review of the references by the Examiner, a copy of the Information Disclosure Statements and the Forms 1449 are attached hereto. Copies of the cited references were provided at the time of filling the original Information Disclosure Statement, and, therefore, no additional copies of the references are submitted herewith. Applicant will be pleased to provide additional copies of the references upon the Examiner's request if it proves difficult to locate the original references.

CONCLUSION

It is believed that all the rejections have been obviated or overcome and the claims are in conditions for allowance. Early notice to this effect is solicited.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those, which may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: **BOX AF,** Commissioner for Patents, Washington, DC 20231, on June 21, 2002.

Nora C. Martinez